ELSEVIER

Journal of Cystic Fibrosis 12 (2013) 92 – 96

Journal of Cystic Fibrosis

www.elsevier.com/locate/jcf

Case Studies

Recurrent *Clostridium difficile* colitis in cystic fibrosis: An emerging problem

Katarine Egressy, Michaelene Jansen, Keith C. Meyer *

Section of Allergy, Pulmonary, and Critical Care Medicine, Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, United States

Received 3 May 2012; accepted 26 May 2012
Available online 19 June 2012

Abstract

Objective: To examine the incidence of recurrent *Clostridium difficile* infection in patients with cystic fibrosis (CF), including patients who had undergone lung transplantation, and review clinical findings in hospitalized patients with *C. difficile* colitis.
Methods: A retrospective chart review was performed to examine the clinical presentation and management of patients with cystic fibrosis (CF) who received care at the University of Wisconsin Hospital and Clinics (UWHC) from 1994 to 2011 and were prospectively identified with *C. difficile* colitis.
Results: Ten cases of *C. difficile* associated disease (CDAD) occurred in patients with CF followed by our Adult CF Center over a period of 17 years, and 4 patients were bilateral lung transplant recipients. Two of the lung transplant recipients had recurrent CDAD that lead to fulminant pancolitis, surgical intervention, and shock. Two patients in the non-transplant group experienced recurrent *C. difficile* infection that led to fulminant pancolitis with associated systemic inflammatory response syndrome and required colectomy.
Conclusions: C. difficile colitis can cause life threatening illness in patients with CF, and symptoms may be subtle and/or atypical and lead to significant delay in diagnosis. Patients with recurrent *C. difficile* colitis are at high risk of fatal outcome, and empiric therapy should be considered for patients with previous *C. difficile* colitis even in the absence of disease when broad-spectrum antibiotics are given to treat bacterial infection.

Keywords: Clostridium difficile; Pseudomembranous colitis; Cystic fibrosis; Lung transplantation

1. Introduction

Clostridium difficile infection primarily occurs in hospitalized patients, causing as many as 3 million cases of diarrhea and colitis per year [1]. Although the overall reported incidence of *C. difficile* colitis in cystic fibrosis patients continues to be low, positive stool cultures for *C. difficile* have been reported in up to 43% of individuals with CF, but patients with toxin-producing strains tend to remain asymptomatic [2]. According to Theunissen et al. [3] patients with CF who were lung transplant recipients had a higher risk of developing *C. difficile* infection and tended to present with atypical clinical symptoms. Since 1996 multiple case review studies have highlighted the serious nature of *C. difficile* associated disease (CDAD) in patients with CF. Yates et al. [4] suggested that immunosuppression may play a role in the variable presentation of CDAD and is likely to be important in the pathogenesis of the disease by increasing the risk of colonization. As more patients with severe CF lung disease undergo lung transplantation, failure to diagnose CDAD in a timely manner may lead to high morbidity and mortality [5]. Several risk factors have been shown to be associated with CDAD in patients with CF including recent antibiotic use, impaired immunity and decreased gastric acidity. A genotype link (N1303K mutation) that may increase susceptibility to CDAD has been described between CF and *C. difficile* [6]. However, despite the frequent antibiotic use in patients with CF, the incidence of CDAD remains relatively low. However, with the advent of lung transplantation, severe, often asymptomatic CDAD cases may occur, and heightened vigilance and clinical suspicion are required to make an early diagnosis, provide effective therapy, and prevent complications.

* Corresponding author. Tel.: +1 608 263 6363(office), +1 608 263 3035(secretary); fax: +1 608 263 3104.
E-mail address: kcm@medicine.wisc.edu (K.C. Meyer).

1569-1993/$ -see front matter
doi:10.1016/j.jcf.2012.05.007

2. Methods

We performed a retrospective chart review of ten cases of CDAD that occurred between 1994 and 2010 in patients with CF followed by our Adult CF Center. We specifically examined the clinical course and management of 4 patients with severe disease, of whom 2 were lung transplant recipients. Patient demographics are given in Table 1, and outcomes are given in Table 2. This research was approved by the University of Wisconsin Human Subjects Committee. The University of Wisconsin—Madison Health Sciences Minimal Risk IRB has granted exemption for this research on March 7, 2012 under category 45 CFR 46.101(b) [4].

3. Results

3.1. Pretransplant CF patients

3.1.1. Case 1

A 23-year-old female with chronic *Pseudomonas aeruginosa* respiratory tract colonization was emergently transferred to our hospital for evaluation of abdominal pain, nausea and vomiting that began 1 week after having been discharged following treatment for a CF respiratory exacerbation with intravenous tobramycin and piperacillin/tazobactam. Upon admission to our facility she was found to have disseminated intravascular coagulation and septic shock thought to be related to fulminant colitis (Fig. 1). Empiric treatment with intravenous and enteric vancomycin, as well as intravenous metronidazole was initiated. She was taken to the OR on the day of admission for subtotal colectomy with end ileostomy. One week post-operatively she was transferred back to the intensive care unit for cardiac arrythmia, hypotension and fever. Recurrence of *C. difficile* infection in the rectal stump was confirmed. Treatment with oral and rectal vancomycin and intravenous metronidazole was initiated. She recovered and was discharged, and she eventually had a successful re-anastomosis of her ileum and rectum 6 months following her initial admission.

3.1.2. Case 2

A 31-year-old female with chronic respiratory tract *P. aeruginosa* colonization presented with abdominal discomfort and cramping for 4 days. She had received intravenous tobramycin, aztreonam, and vancomycin 1 month prior to admission for a CF respiratory exacerbation and had undergone endoscopic sinus surgery. Her abdominal plain film showed an unremarkable air pattern in the colon without signs to suggest toxic megacolon. Stool culture could not be obtained on admission due to constipation. On the basis of her clinical presentation, empiric therapy with intravenous and oral vancomycin and metronidazole was begun. The patient continued to experience abdominal pain, edema and fever. Due to failure of conservative management and development of an acute surgical abdomen she was taken to the operating room for an exploratory laparotomy with subsequent subtotal colectomy and end ileostomy. Pseudomembranous colitis was clearly demonstrated in the resected colon. She developed multi-organ failure and persistent shock post-operatively and was given activated protein C therapy. Persistent ileus developed post-operatively, and treatment with oral vancomycin and intravenous metronidazole was continued throughout her hospitalization due to concerns of persistent *C. difficile* infection. Eventually the patient was transitioned to oral vancomycin alone as her bowel function improved and was discharged from the hospital. She underwent ileostomy takedown and reanastomosis of ileum to rectum without complications 7 months later.

Table 1
Patient demographics.

Parameter	Transplant	Non-transplant
Total N	4	6
Gender (M/F)	2/2	4/2
Mean age (years)	38.3	25.8

3.2. Lung transplant recipients

3.2.1. Case 3

A 37-year-old male with CF and chronic *P. aeruginosa* colonization had an unremarkable clinical course following bilateral lung transplantation and was started on standard tacrolimus-based immunosuppression. Six months later he presented to the hospital with persistent fatigue, nausea, vomiting and failure to thrive. Hospital evaluation revealed a pancolitis that was thought to be secondary to *C. difficile* although stool cultures were negative at that time. The patient was treated with oral and intravenous vancomycin and slowly improved. One month later he presented with diarrhea and hypotension. A colonoscopy demonstrated edematous colonic mucosa with the presence of diffuse pseudomembranes. Due to his fulminant pancolitis and septic shock, a subtotal colectomy with ileostomy was performed. Unfortunately, the patient was unable to wean from the ventilator and continued to require intravenous pressors for systemic hypotension. He was maintained on broad-spectrum antibiotics despite his diagnosis of *C. difficile* colitis due to development of probable hospital-acquired pneumonia and gangrenous cholecystitis. He subsequently required a return to the operating room due to persistent necrotizing cholecystitis and small bowel obstruction. Due to lack of clinical improvement and progression of multi-organ failure, he was transitioned to comfort care and expired 8 days later.

3.2.2. Case 4

A 43-year-old female had several hospitalizations over a period of several months for recurrent episodes of cholangitis with cholelithiasis due to antibiotic-resistant *P. aeruginosa* 13 years post-bilateral lung transplant and 5 years post kidney transplant. Her immunosuppression was cyclosporine-based, and she received multiple broad-spectrum antibiotics including intravenous vancomycin and colistimethate due to recurrent cholangitis and was finally hospitalized for increasing abdominal pain. Abdominal imaging demonstrated multiple dilated bowel loops with wall thickening concerning for pseudomembranous colitis (Fig. 2). The patient was placed on intravenous metronidazole and oral vancomycin. Her immunosuppressants were held and the patient was given intravenous pulse-dose steroids with 60 mg of intravenous solumedrol. She gradually

Table 2
Presenting symptoms, laboratory values and treatment modalities for all CF patients with CDAD.

Case	Age	Previous antibiotic pressure	Symptoms	Initial WBC count	Presence of shock	Colectomy	Treatment	Recurrence	Outcomes
1	23	Yes	Cramping, loose stools	3.6	Yes	Yes	Oral and rectal vancomycin, intravenous metronidazole	Yes	Survived
2	31	Yes	Abdominal pain	12.1	Yes	Yes	Oral vancomycin and intravenous metronidazole	Yes	Survived
3	37	Yes	Fatigue, diarrhea	6.1	Yes	Yes	Oral and intravenous vancomycin	Yes	Deceased
4	43	Yes	Abdominal pain, loose stools	4.5	No	No	Oral rifaximin, IVIG, oral and rectal vancomycin, intravenous and oral metronidazole	Yes	Survived
5	39	No	Nausea, vomiting	NA	No	No	Oral vancomycin and intravenous metronidazole	No	Survived
6	56	Yes	Diarrhea	8.4	No	No	Oral vancomycin and intravenous gancyclovir	No	Survived
7	42	Yes	Loose stools	7.4	No	No	Oral vancomycin and intravenous gancyclovir	No	Survived
8	27	Yes	Nausea, diarrhea	8.9	No	No	Oral vancomycin and intravenous gancyclovir	No	Survived
9	33	Yes	Diarrhea	6.9	No	No	Oral vancomycin	No	Survived
10	26	Yes	Vomiting, malaise, diarrhea	11.2	Yes	No	Oral vancomycin and intravenous metronidazole	No	Deceased

Initial WBC count = white blood cell count $\times 10^3/\mu l$; NA = not available.

improved and was discharged home on metronidazole 500 mg three times daily, vancomycin 125 mg po 4 times daily for 1 month along with her post-transplant immunosuppressive and antifungal medications. She continued to have frequent loose stools and her symptoms worsened when her oral vancomycin was stopped. One week later she was readmitted for suspected recurrent CDAD. A repeat stool specimen was positive for *C. difficile*. Given the refractory nature of her *C. difficile* infection she was treated with a variety of regimens including oral rifaximin, vancomycin enemas, intravenous immunoglobulin course of 5 days, and intravenous metronidazole and fecal transplant were considered. Liver transplantation was considered for her persistent cholangitis and hepatic cirrhosis if the *C. difficile* infection cleared. However, both the cholangitis and CDAD gradually cleared without the need for surgical intervention, and she has not had any recurrence for over 2 years.

4. Discussion

At present the interaction between *C. difficile* and immune defenses is poorly understood, and the majority of patients who have ingested *C. difficile* spores remain well. It has been shown that patients who develop antibodies to *C. difficile* after the bacterium is present in the bowel are less likely to develop CDAD. While most cases of CDAD are mild to moderately severe, it is not clear why some cases are fulminant, resulting in rapid progression to severe and potentially fatal disease, and the transition of mild disease to fatal infection is unpredictable. Systemic symptoms do not appear to be derived from bacteremia, colonic perforation, or ischemia, but from toxin-induced inflammatory mediators (interleukin-8, macrophage-inflammatory protein-2, substance P, tumor necrosis factor-alpha) released locally in the colon [7,8]. Age, immune responsiveness, type of antibiotic exposure, anti-cancer chemotherapy, strain differences in toxin production, and delays in

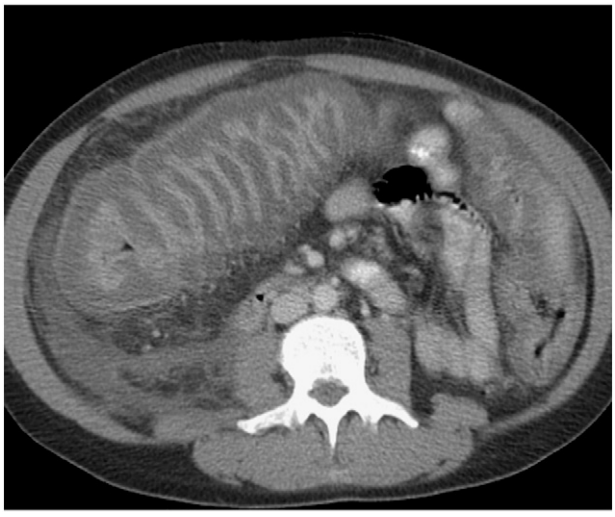

Fig. 1. Abdominal computed tomogram of a patient with significant colonic distention, bowel wall thickening and severe CDAD (case #1).

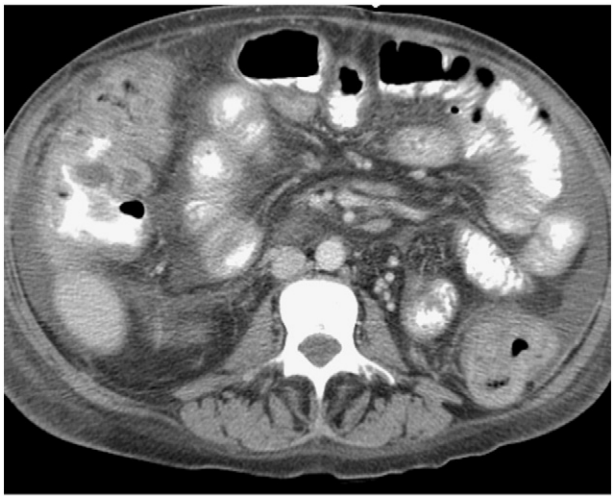

Fig. 2. Abdominal computed tomogram with colonic wall thickening, air fluid levels and abdominal ascitic fluid in a patient with CDAD (case #4).

diagnosis and treatment are all thought to be factors that affect the outcome of infection. Factors leading to relapse of CDAD are also not well understood at present, but persistent imbalance of the normal bowel bacterial biome is suspected to be one of many possible causes of relapse. It is well known that *C. difficile* spores persist in the colon following successful treatment of diarrhea [9].

Due to the alteration in the CFTR ion channel, patients often present with atypical symptoms and the diagnosis of *C. difficile* colitis can be missed. Often a patient is unable to provide a stool sample to verify the findings of *C. difficile* colitis suggested by diagnostic studies due to constipation. Despite heavy antimicrobial pressure, patients with CF have a low incidence of CDAD as we have observed in our own institution. We describe a unique presentation of four cases of patients with CDAD and CF due to the recurrence of CDAD as an entity that is much harder to treat and led to fulminant colitis and death in case 3.

Recurrent CDAD has been described in patients with CF, but this entity is not fully characterized in the available literature and presents a challenge to the clinician. Its occurrence can lead to prolonged antimicrobial treatment, and novel treatment options such as intravenous immunoglobulin or stool transplantation have been given [10]. Table 2 demonstrates that 9 of our 10 patients had previous (i.e. within a month of presentation) antibiotic exposure that included intravenous tobramycin, as all of our patients had known Pseudomonas respiratory infection. Additionally, two out of the 10 patients presented with atypical symptoms, and 7 patients presented with normal leukocyte count despite documented *C. difficile* infection. We noted a similar incidence of shock in non-transplanted patients versus lung transplant recipients (Fig. 3). However, a lower recurrence rate was observed in the non-transplant cohort. In addition we observed a clustering of CDAD infection in cases 8–10, which was probably due to temporal proximity of hospital admission and nosocomial spread of *C. difficile* spores.

Two of the 10 cases had fatal outcome. Previous reports of 50% mortality as reported by Yates et al. highlight the importance of vigilance to detect the presence of *C. difficile*, and therapy for *C. difficile* infection should be started immediately when it is suspected to be present pending confirmation of the *C. difficile* toxin in stool samples, as these patients can rapidly develop critical illness and are at high risk of death [11,12].

Current literature recommends treatment with metronidazole or vancomycin for 10–14 days, and significant improvement in symptoms should be observed within 48–72 h [13]. In addition, novel treatments such as intravenous immunoglobulin, oral rifaximin and stool transplantation have been described. Patients who do not respond to medical therapy will require surgical intervention and long term antibiotic prophylaxis to ensure disease-free survival. Radiographic modalities such as computed tomography of the abdomen, abdominal magnetic resonance imaging, and abdominal ultrasound have been used as adjunct diagnostic tools in diagnosis of *C. difficile* colitis, and abdominal imaging and endoscopic examination of the colon were used to ascertain the diagnosis. We used abdominal CT scanning as well as direct visualization of colonic mucosae via enteroscopy to ascertain the diagnosis in 4 of the 10 patients in our series.

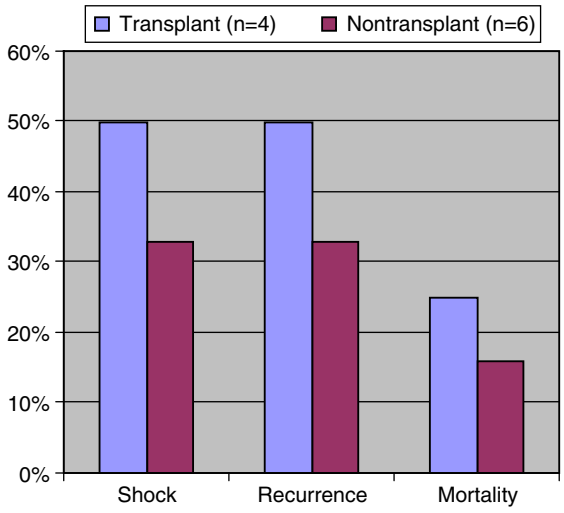

Fig. 3. Comparison of shock, recurrence of CDAD and overall mortality in transplanted versus non-transplanted CF patients (n=10).

5. Summary and conclusions

We present a series of ten patients with CDAD that has led to recurrence in four out of ten patients and subsequent development of shock, sepsis and the need for surgical intervention. Although we do not demonstrate a 50% mortality rate previously as described in a lung transplant CF population, the role of immunosuppression likely remains important in the pathogenesis of disease by increasing the risk of colonization, as highlighted by the series of Dallal et al. [14]. The presentation of CDAD can be mistaken for other diagnoses such as distal intestinal obstruction syndrome (DIOS), meconium ileus, appendicitis, pancreatitis, constipation, gastrointestinal malignancy, ovarian cyst, volvulus, bowel adhesions, intussusception and inflammatory bowel disease states. Despite the broad differential diagnosis, a high index of clinical suspicion and radiographic modalities such as computed abdominal scans and magnetic resonance imaging allow the clinician to make an accurate diagnosis of CDAD. As demonstrated in our series, despite appropriate medical and surgical treatment CDAD may reoccur and lead to significant clinical morbidity and mortality. This specifically is demonstrated by increased rates of recurrence in the lung transplant population in our series as 50% of CDAD cases in lung transplant patients recurred however only 33% of non-lung transplant patients demonstrated recurrence as demonstrated in Fig. 3. This study corroborates the previous data by Dallal et al. [14], showing that immunosuppression as part of lung transplantation and/or previous history of treatment for *C. difficile* colitis increases the risks of CDAD recurrence and possibly mortality and morbidity. Therefore, we propose that empiric anti *C. difficile* treatment should be used in lung transplant patients with previous history of CDAD despite absence of symptoms during hospitalizations. Further studies are necessary to confirm this conclusion.

None of the contributing authors of this manuscript have a financial interest or a proprietary interest in the research, such as royalties, patents, trademarks, copyright, or licensing agreement,

that is relevant to this research study (including any agent, device, or software being evaluated as part of the research study).

Acknowledgment

This research was supported in part by the George and Julie Mosher Pulmonary Research Fund.

Katarine Egressy, MD, MPH conducted chart review, data analysis, and manuscript writing and editing.

Michaelene Jansen, PhD, APNP conducted preliminary chart review, data analysis, and preliminary manuscript writing and editing.

Keith C. Meyer, MD, MS, FCCP, FACP conducted chart review, data analysis, and manuscript writing and editing. Dr. Meyer is the guarantor of this manuscript.

References

[1] Peach SL, Borriello SP, Gaya H, Barclay FE, Welch AR. Asymptomatic carriage of *Clostridium difficile* in patients with cystic fibrosis. J Clin Pathol Sep 1986;39(9):1013–8.

[2] Binkovitz LA, Allen E, Bloom D, Long F, Hammond S, Buonomo C, et al. Atypical presentation of *Clostridium difficile* colitis in patients with cystic fibrosis. AJR Am J Roentgenol Feb 1999;172(2):517–21.

[3] Theunissen C, Knoop C, Nonhoff C, Byl B, Claus M, Liesnard C, et al. *Clostridium difficile* colitis in cystic fibrosis patients with and without lung transplantation. Transpl Infect Dis Jul 2008;10(4):240–4 [Epub 2007 Jul 12].

[4] Yates B, Murphy DM, Fisher AJ, Gould FK, Lordan JL, Dark JH, et al. Pseudomembranous colitis in four patients with cystic fibrosis following lung transplantation. Thorax Jun 2007;62(6):554–6.

[5] Dallal RM, Harbrecht BG, Boujoukas AJ, Sirio CA, Farkas LM, Lee KK, et al. Fulminant *Clostridium difficile*: an underappreciated and increasing cause of death and complications. Ann Surg Mar 2002;235(3):363–72.

[6] Rivlin J, Lerner A, Augarten A, Wilschanski M, Kerem E, Ephros MA. Severe *Clostridium difficile*-associated colitis in young patients with cystic fibrosis. J Pediatr Jan 1998;132(1):177–9.

[7] Flegel WA, Müller F, Däubener W, Fischer HG, Hadding U, Northoff H. Cytokine response by human monocytes to *Clostridium difficile* toxin A and toxin B. Infect Immun Oct 1991;59(10):3659–66.

[8] Castagliuolo I, Keates AC, Wang CC, Pasha A, Valenick L, Kelly CP, et al. *Clostridium difficile* toxin A stimulates macrophage-inflammatory protein-2 production in rat intestinal epithelial cells. J Immunol Jun 15 1998;160(12):6039–45.

[9] http://www.infectioncontroltoday.com/articles/2007/05/cdad.aspx.

[10] Patriarchi F, Rolla M, Maccioni F, Menichella A, Scacchi C, Ambrosini A, et al. *Clostridium difficile*-related pancolitis in lung-transplanted patients with cystic fibrosis. Clin Transplant Jan–Feb 2011;25(1): E46–51, doi:10.1111/j.1399-0012.2010.01316.x.

[11] Riddle DJ, Dubberke ER. *Clostridium difficile* infection in solid organ transplant recipients. Curr Opin Organ Transplant Dec 2008;13(6): 592–600.

[12] Schmitt-Grohé S, Wiggert E, Steffan J, Handke R, Zielen S. Severe antibiotic-associated colitis in a patient with cystic fibrosis and colonic wall thickening. J Pediatr Gastroenterol Nutr Feb 2002;34(2):224–6.

[13] David N, Gilbert DN, Moellering RC, Eliopoulos GM, Sande MA. The Sanford guide to antimicrobial therapy 2007. 37th edn. USA: Antimicrobial Therapy, Inc.; 2007. p. 16.

[14] Dallal RM, Harbrecht BG, Boujoukas AJ, Sirio CA, Farkas LM, Lee KK, Simmons RL. Fulminant *Clostridium difficile*: an underappreciated and increasing cause of death and complications. Ann Surg Mar 2002;235(3): 363–72.